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MICROCHIP COCRYSTALLIZATION WITH SUPERCRITICAL CO₂

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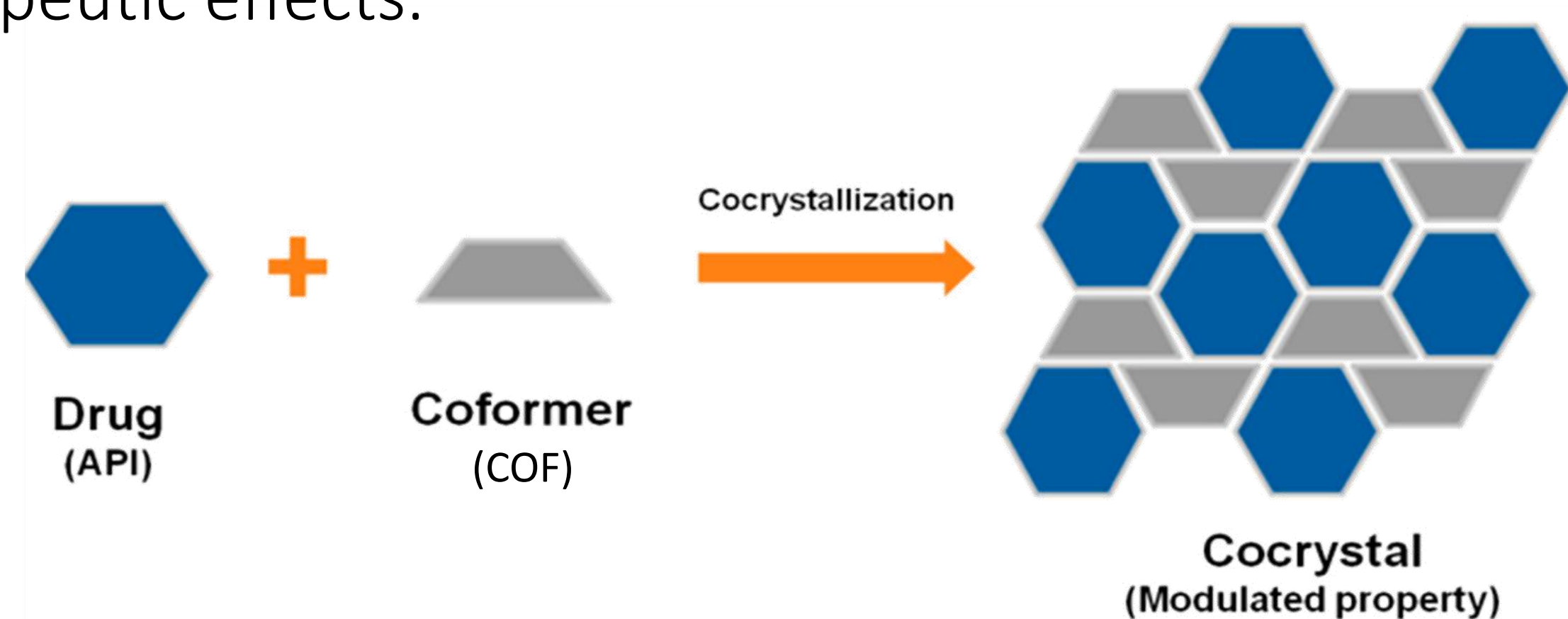
1 CONTEXT

Introduction

What is a cocrystal ?

In the pharmaceutical field, a cocrystal is a solid with a single crystalline phase composed of two entities : the **active pharmaceutical ingredient (API)** and the **coformer (COF)**.

Cocrystals are produced in order to enhance drugs physicochemical properties by incorporation of the coformer into their crystalline structure, without altering therapeutic effects.



Supercritical CO₂ as an anti-solvent

Anti-solvent effect

The system {API+COF} is preliminarily dissolved into a solvent miscible with CO₂, then the solubility of the solution is reduced by adding supercritical CO₂.

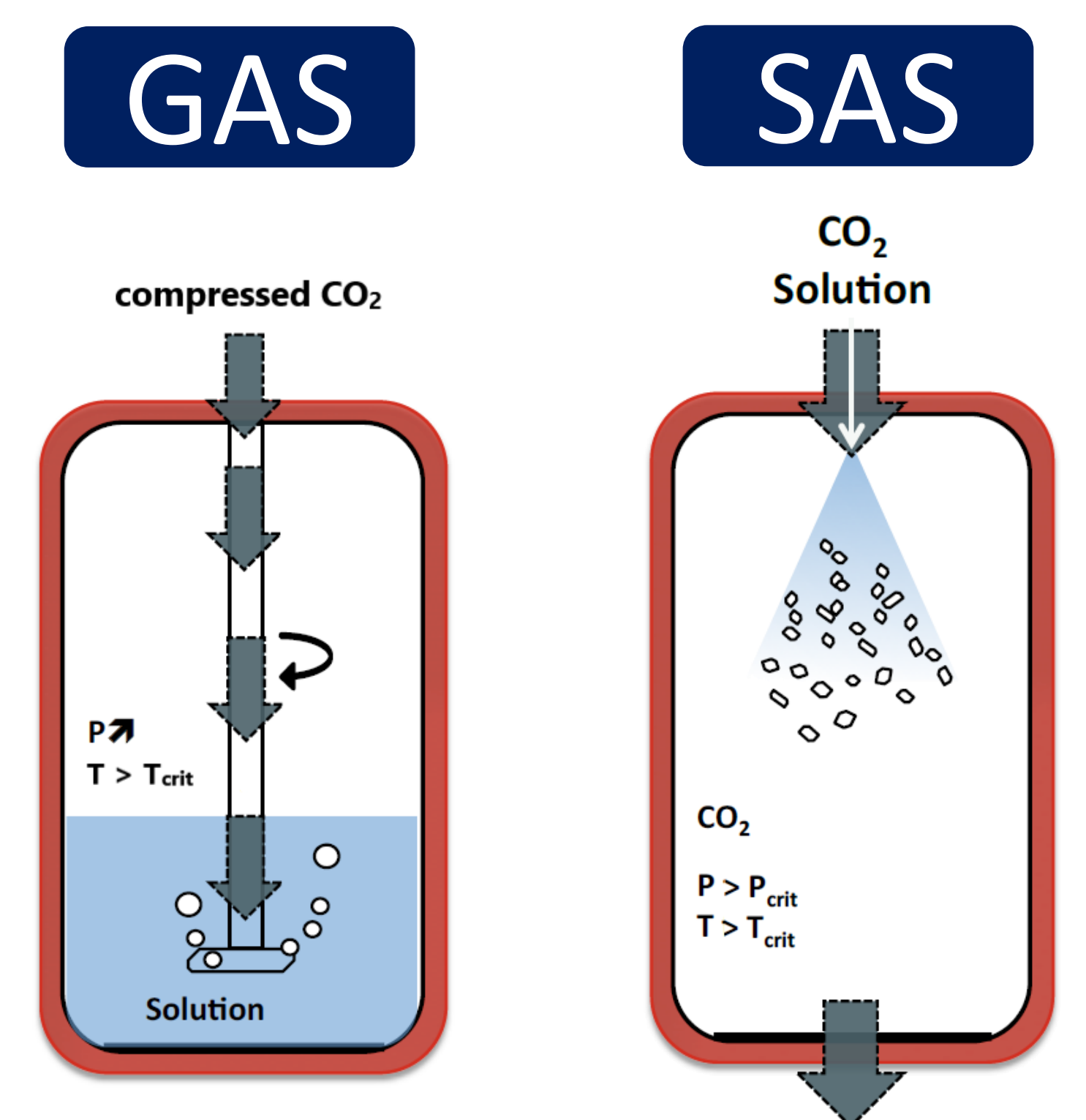
Two main scCO₂ precipitation methods

Gasous Anti-Solvent (GAS) :

scCO₂ is added gradually into the solution {solvent+API+COF}

Supercritical Anti-Solvent (SAS) :

The solution {solvent+API+COF} is injected into a continuous flow of scCO₂



[C. Neurohr, PhD Thesis, 2015]

ANY VISUAL OBSERVATIONS FOR TIME-RELATED EVENT ANALYSIS

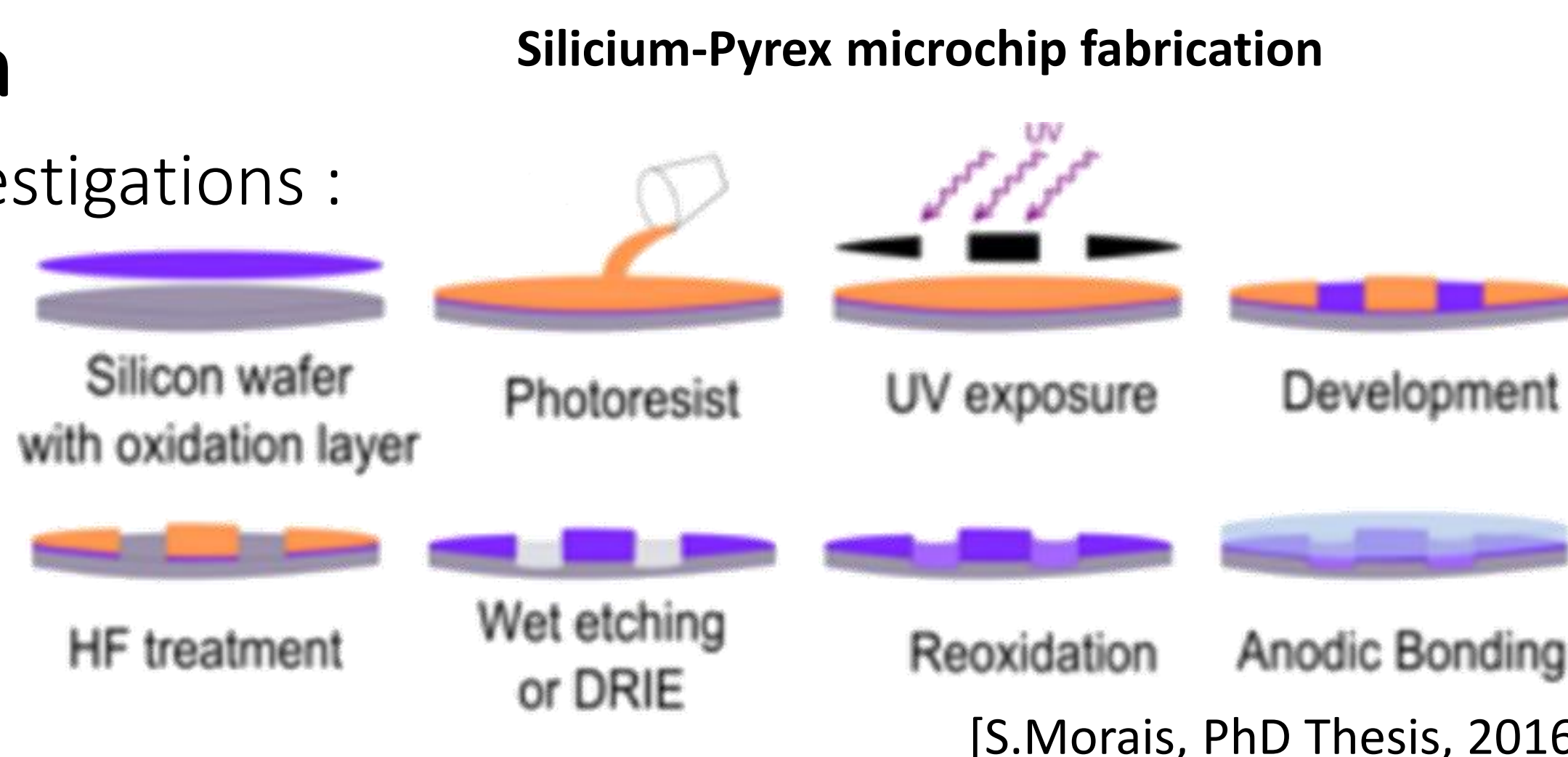
2 METHODOLOGY

Microfluidic approaches

Silicium-Pyrex on-chip cocrystallization

Microfluidic platforms are great tools for cocrystal investigations :

- Fast screening capability
- High reproducibility
- Control on hydrodynamics
- Improved heat and mass transfers
- **In-situ on-chip analysis under high pressure**



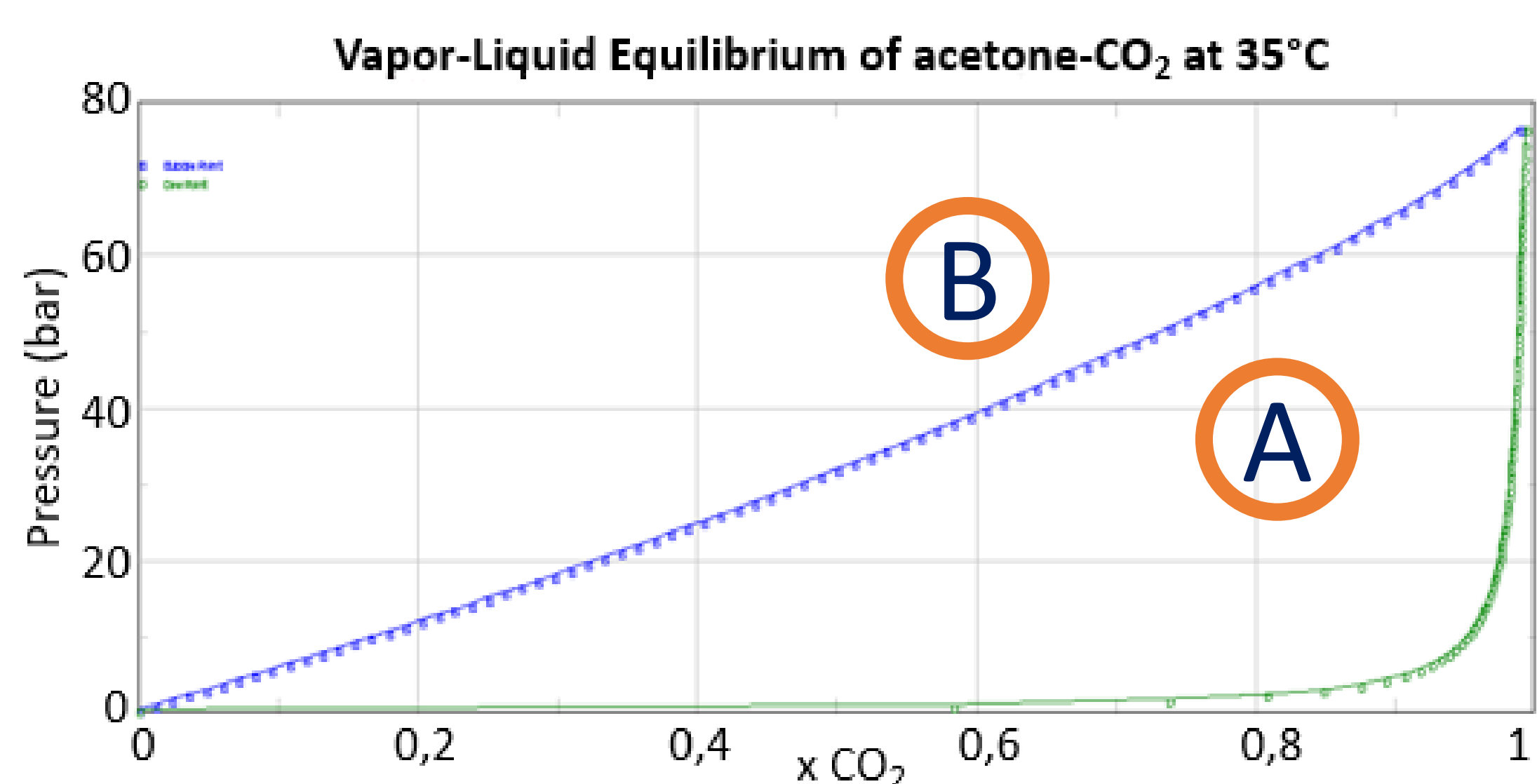
OBJECTIVES

- ❖ Access to time-related events (kinetics / diffusion / induction time) by studying nucleation and growth of cocrystals in microfluidic platforms thanks to in-situ analysis and observations
- ❖ Control crystal phase structure

Strategies for microchip design & Preliminary results

Strategies

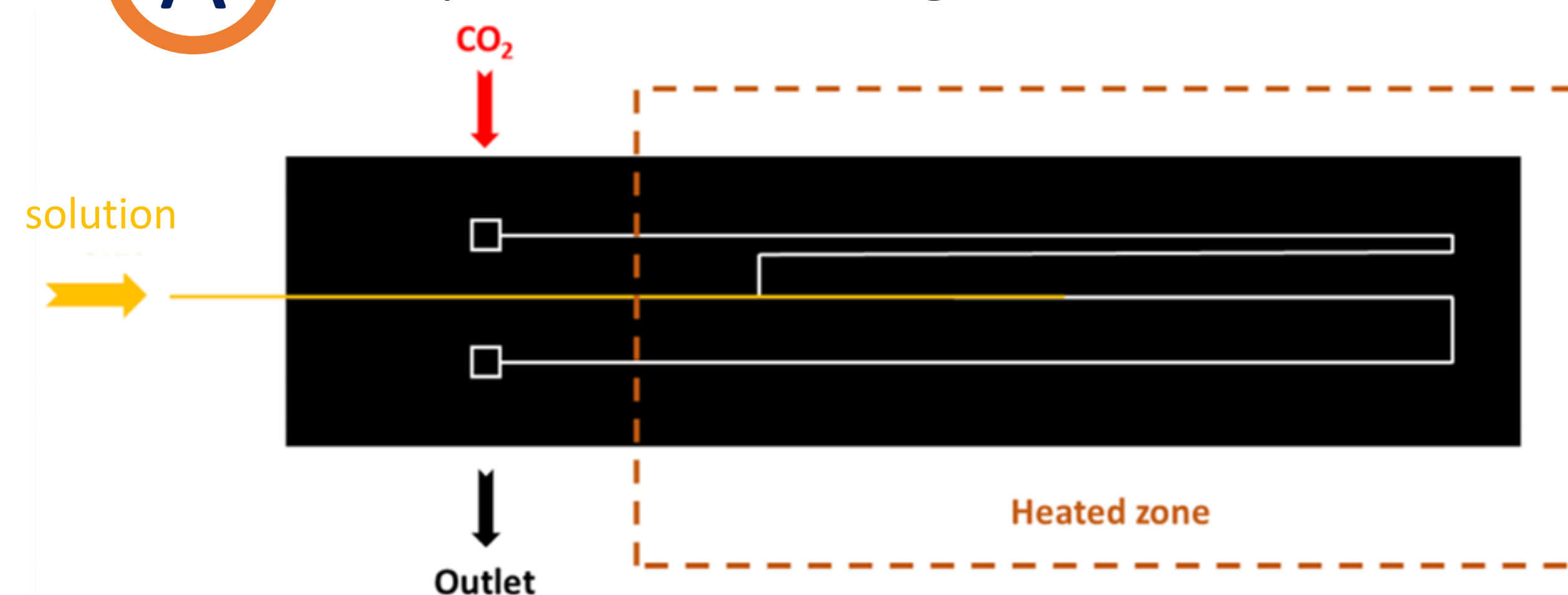
Solvent-CO₂ thermodynamic data are essential for the development of microchips



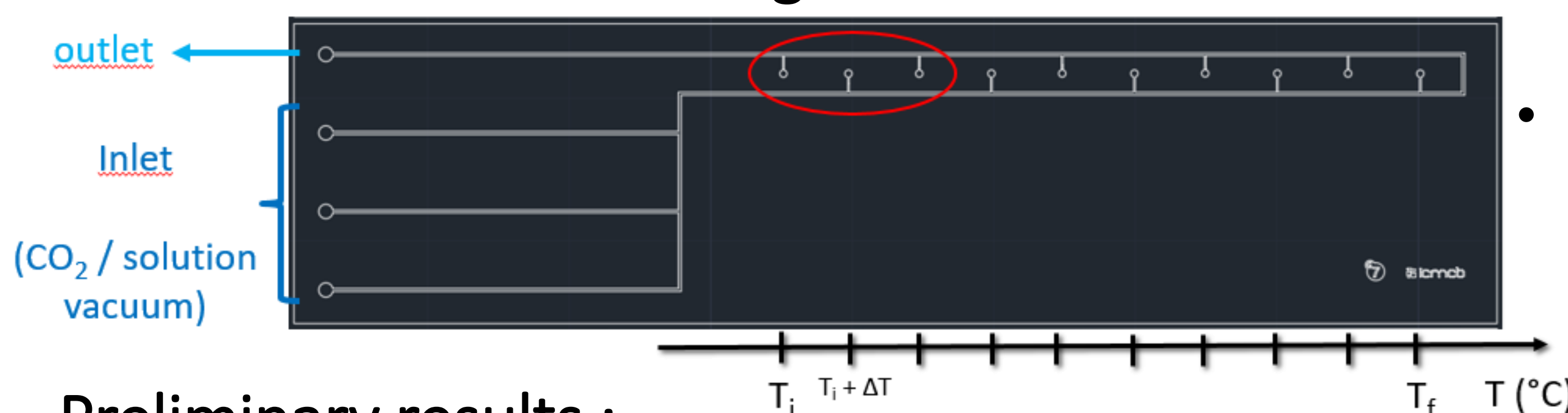
A Biphasic conditions : generation of {solvent+API+COF} droplets surrounded by scCO₂

B Monophasic conditions : immobilize solution {solvent+API+COF} in wells and fill the main channel with scCO₂

A Droplet-based design



B Well-based design with a temperature gradient



Preliminary results :

Working conditions with design **B** :

P = 80 bar / T = 35°C

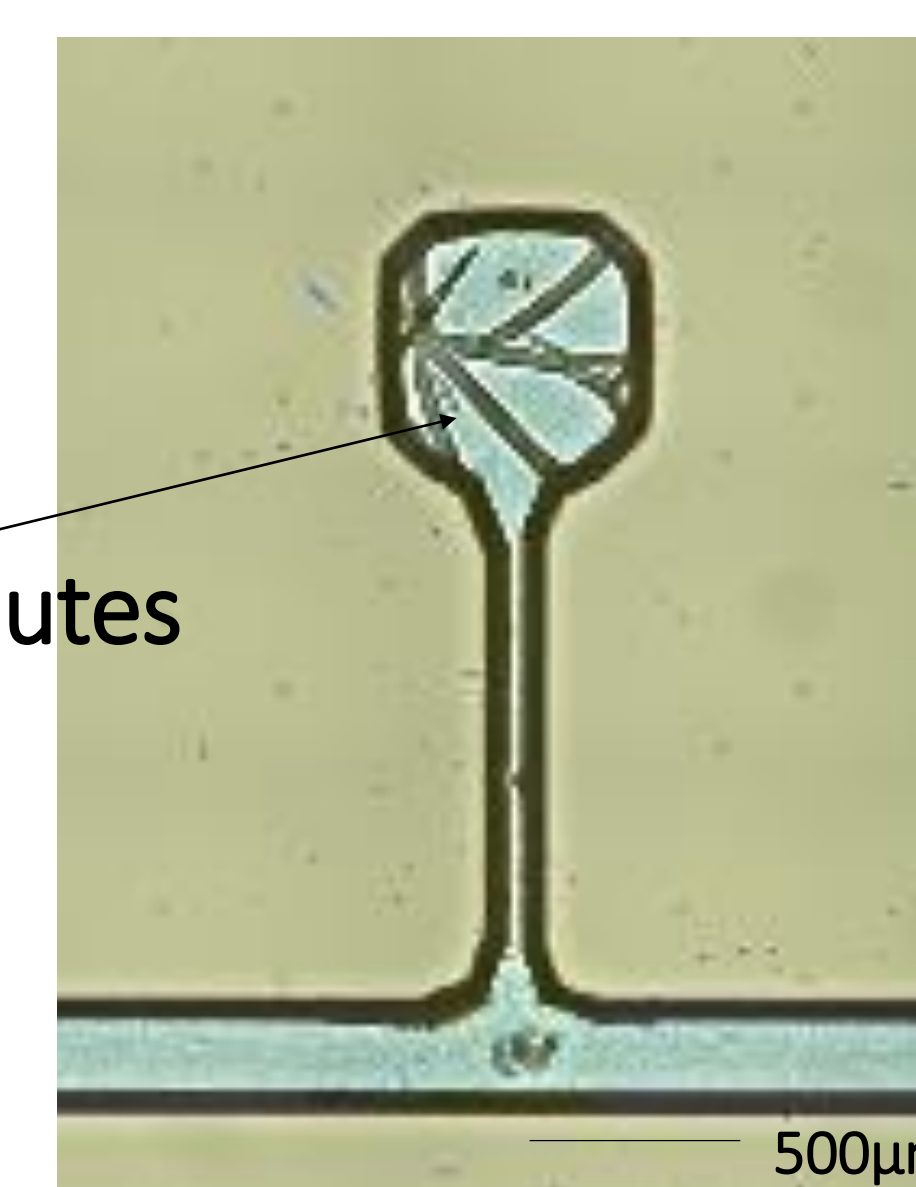
Solvent = acetone

API = Naproxen

COF = nothing

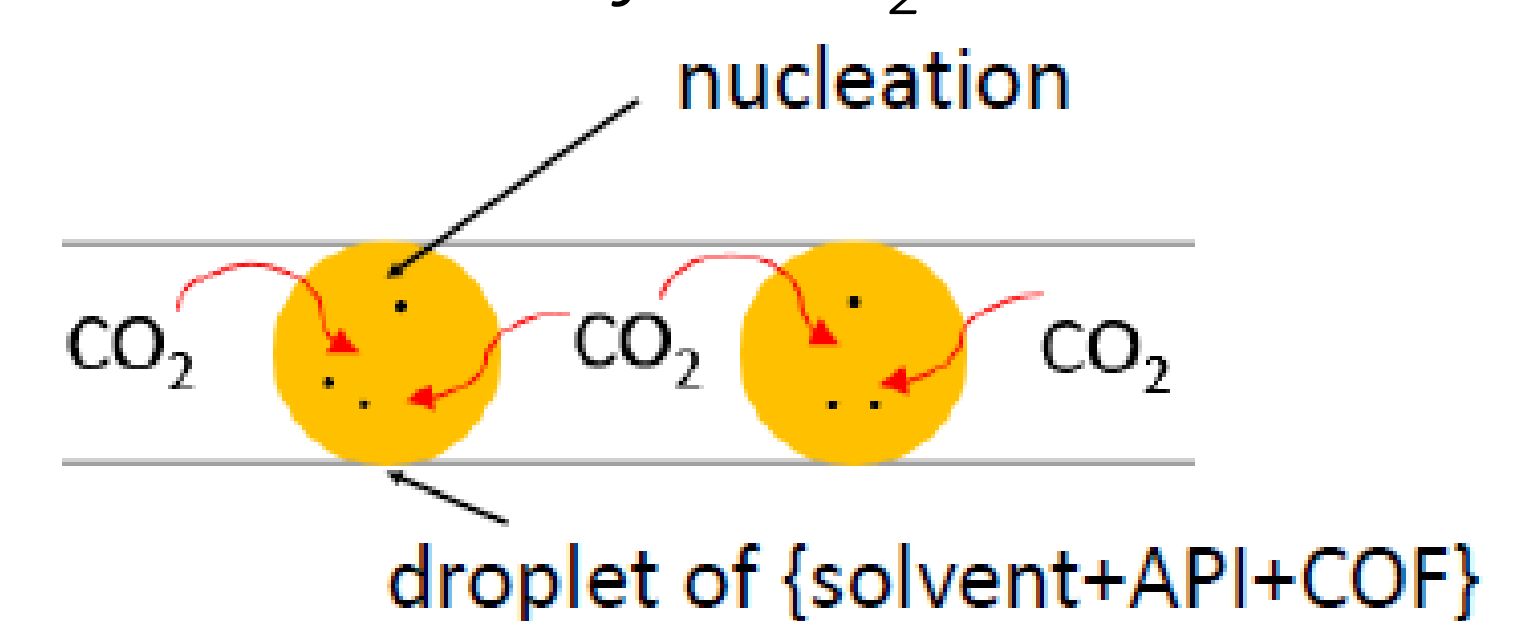
Needles of naproxen

Induction time < 3minutes



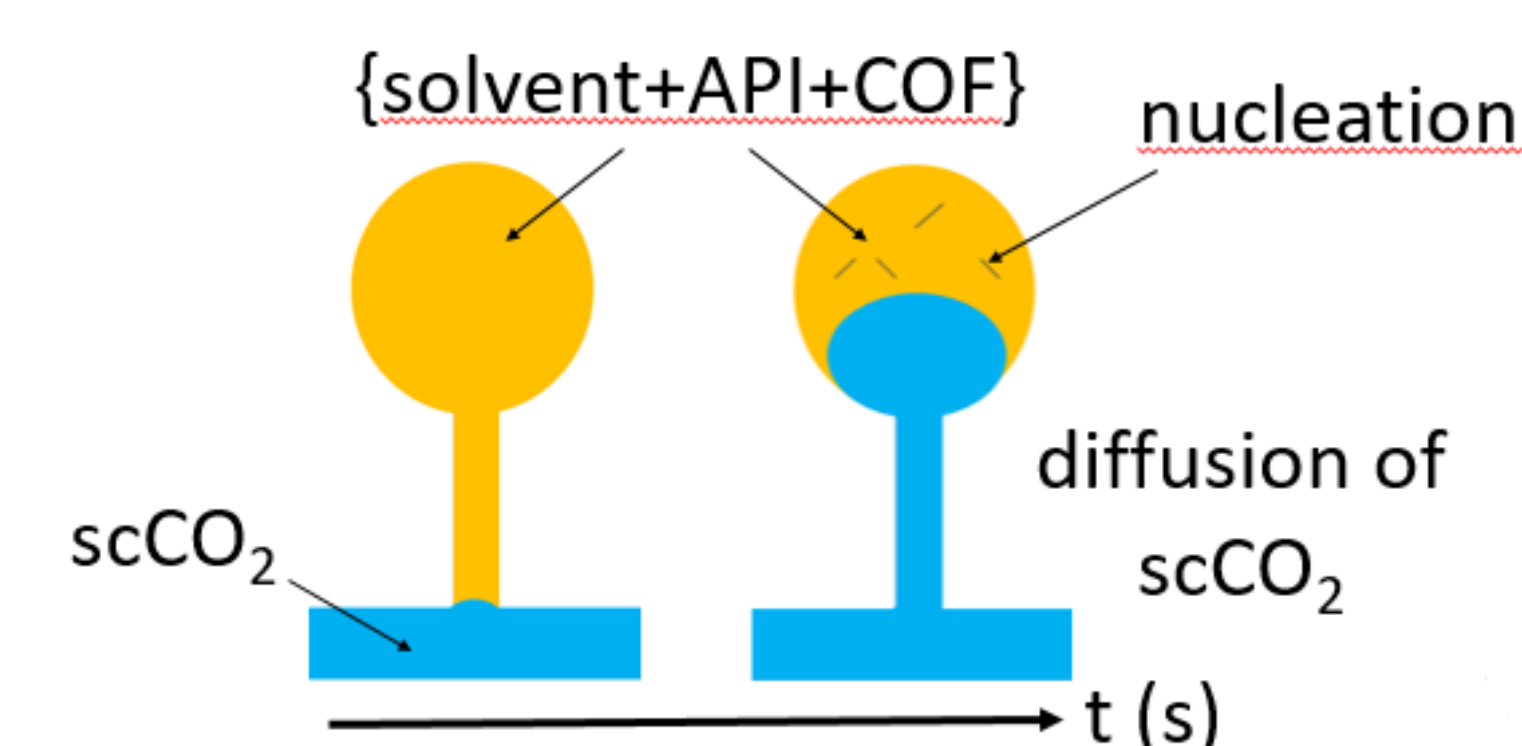
Aim

- Stabilization of droplets into a flux of scCO₂



For both design, nucleation will occur with diffusion of scCO₂ into the « microreactor »

- Immobilization of solution into wells



3 CONCLUSION

Combination of microfluidic tools and knowledge on cocrystallization in compressed CO₂ led to have information on precipitation processes like composition, diffusion and induction time by using *in-situ* analysis technologies.